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10/016,752	10/30/2001	Ramy Lidor-Hadas	1662/55002	8981

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EXAMINER

OH, TAYLOR V

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application N .

10/016,752

Applicant(s)

LIDOR-HADAS ET AL.

Examiner

Taylor Victor Oh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 5-8 and 10-93 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5-8 and 10-93 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

## **Final Rejection**

### **The Status of Claims**

Claims 5-8, and 10-93 are pending.

Claims 5-8, and 10-93 have been rejected.

### **Claim Objections**

The objection of the claims 18 and 72 has been withdrawn due to the modification made in the amendment.

### **Claim Rejections - 35 USC 102**

The rejection of Claims 21-22, 49-50, 52, 57-58, 66-67, and 74-76 under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234) has been maintained due to applicants' failure to change the claim languages.

The rejection of Claims 19-20, 23,39-45, 62-65, 71, and 87-91 under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234) has been changed to the rejection of Claims 19-20, 23,39-45, 62-65, 71, and 87-91 under 35 U.S.C. 103 (a) as being unpatentable over Wu Gousheng et al (CN 1113234).

### **Claim Rejections - 35 USC 103**

1. Applicants' argument filed 7/9/2003 have been fully considered but are persuasive.

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Rejection of Claims 5-8, 10-18, 24-38, 46-48, 51, 53-56, 59-61, 68-70 77-86, 92  
are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN  
1113234).

The rejection of Claims 5-8, 10-18, 24-38, 46-48, 51, 53-56, 59-61, 68-70 77-86, 92  
are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN  
1113234) is maintained for the reasons of the record in paper no. 11.

***Claim Rejections - 35 USC § 103***

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19-20, 23,39-45, 62-65, 71, and 87-91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN 1113234).

Wu Gousheng et al discloses a 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound (see page 16 on its translation ,lines 20-22); furthermore, an organic base and standard physiological salt and solvate can be incorporated into the compound in order to be used as a medication for treating nausea and vomiting (see abstract ). Concerning the production of the 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound, the following steps can be used:

1. dissolving the compound of 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole in 5 ml of ethanol;

2. blowing dry HCl into the solution;
3. cooling down the resultant mixture, crystallizing the compound , and recrystallizing it with water , thereby obtaining the 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound (see page 21 , lines 8-17).

Furthermore, in order to isolate the 1,1,2,2,3- pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound, the 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound is recrystallized with water and dried in a drier containing P<sub>2</sub>O<sub>5</sub> (see page 17 , lines 16-17).

Moreover, there is a general procedure for producing the 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride with an aqueous solvent by dissolving the 1,1,2,2,3- pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole to a water /alcohol solvent and adding hydrogen chloride (1N) to the resultant mixture to produce the desired compound (see page 8 , lines 19-24).

However, Wu Gousheng et al differs from the instant invention in that a solvent system contains chloroform, toluene, ketone ,xylene, isopropanol, methyl tert-butyl ether during the process; the exposure is for a period of three weeks or less or 30 to 70 hours; the temperature is from -15<sup>0</sup> C to room temperature; and the mechanical agitation is sonification.

Concerning the use of the various solvent system for producing the desired compound, the reference is silent about them. However, the Wu Gousheng et al does indicate the use of benzene and n-propanol, which are similar to the functionality of the claimed solvents. Therefore, there is no patentable weight over the prior art reference in the absence of an unexpected result using the claimed solvent system.

With respect to the exposing period of three weeks or less or 30 to 70 hours and the temperature is from  $-15^{\circ}\text{C}$  to room temperature, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature and period are well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity of a chemical process.

Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process.

Wu Gousheng et al does teach the general procedure for producing the 1,1,2,2,3-pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride with an aqueous solvent by dissolving the 1,1,2,2,3- pentahydrogen-9-methyl-3( (2'-methyl-imidazole-1)-methyl)-4-oxocarbazole to a water /alcohol solvent and adding hydrogen chloride (1N) to the resultant mixture to produce the desired compound. Furthermore, in order to optimize the reaction conditions such as time and temperature for the process, it would have been obvious to the skilled artisan in the art to

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have motivated to modify the period and temperature to the claimed parameters by routine experimentation, thereby accelerating the reaction process.

Response to Argument

Applicants argue the following issues:

1. with respect to claims 5-7 and 10-18, the teachings of the Wu Gousheng reference would not expect to obtain the monohydrate by contacting the dihydrate with the solvent mixture even if Wu Gousheng motivated them to try and regarding the use of sonication, the examiner has applied a blanket motivation to use sonication as a mechanical expediency ;
2. concerning claim 8, the reference does not suggest that ondansetron hydrochloride monohydrate could be converted to the dihydrate under an atmosphere of 50 % relative humidity ;
3. regarding claim 24, the cited reference fails to provide any motivation to i) prepare a pharmaceutical composition comprising the claimed ondansetron hydrochloride Form B and ii) use such a pharmaceutical composition to treat nausea and / or vomiting;
4. in reference to claims 25-38, one skilled in the art would not expect that anhydrous ondansetron hydrochloride could be produced by treating ondansetron hydrochloride in any state of hydration with dry alcohol;
5. in reference to claims 46-48, Wu Gousheng does not teach using gaseous HCl to prepare the hydrochloride salt in toluene, along with unexpectedly producing a



novel polymorph of ondansetron hydrochloride without any guidance in the reference;

6. in reference to claim 51, there is no specific teaching in Wu Gousheng to modify Embodiment A2 to arrive at novel crystalline Form C;

7. regarding claims 42-56, there is no specific teaching in Wu Gousheng to melt ondansetron hydrochloride in the presence of xylene and then adding the melt to ethanol to produce novel crystalline Form D;

8. in reference to claims 59-61, there is no specific teaching in Wu Gousheng to treat ondansetron hydrochloride with isopropanol to form novel crystalline Form E;

9. regarding claims 68-70, there is no specific teaching in Wu Gousheng to induce precipitation of the hydrochloride salt in the presence of ether, thereby producing novel crystalline Form H;

10. regarding claims 77-86, Wu Gousheng does not teach or suggest exposing ondansetron hydrochloride to methanol as a way of transforming it into a novel solid Form I;

11. concerning claim 92, the Wu Gousheng fails to provide any motivation to i) prepare a pharmaceutical composition comprising the claimed ondansetron hydrochloride with an upper particle size limit of 50 microns and ii) use such a pharmaceutical composition to treat nausea and / or vomiting.

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Applicants' arguments have been noted, but the arguments are not persuasive.

First, regarding the first argument , the Examiner has noted applicants' arguments. However, the Wu Gousheng reference does indicate that there is a teaching of forming ondansetron hydrochloride monohydrate by using ondansetron hydrochloride dihydrate compound under a certain reaction condition. Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process. Therefore, the reference is relevant to the claimed invention.

Second, regarding the second argument , the Examiner agrees.

Third, regarding the third argument , the Examiner has noted applicants' arguments. However, claim 24 depends on the canceled claim 1-4 and 9; the claim is objected. Therefore, the claim 24 has not been treated on the merits.

Fourth, regarding the fourth argument , the Examiner has noted applicants' arguments. However, the Wu Gousheng reference does indicate that there is a general teaching of forming anhydrous ondansetron hydrochloride by following a generic procedure (see page 8, lines 19-24). Therefore, the reference is relevant to the claimed invention.

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Fifth, regarding the fifth argument, the Examiner has noted applicants' arguments. However, the current invention is not directed to the formation of polymorphs of ondansetron hydrochloride. Therefore, the reference is still relevant and applicable to the rejection of the claimed invention.

Sixth, regarding the six through nine arguments, the Examiner has noted applicants' arguments. However, the current invention is not directed to the formation of polymorphs of ondansetron hydrochloride. Furthermore, the Examiner recommends that there should be two separate inventions to be filed: one with novel procedures for forming ondansetron hydrochloride hydrates or its anhydrous form; the other with novel procedures for forming polymorphs of ondansetron hydrochloride in various forms. It is well-known in the art that a polymorph can not be in anhydrous form but has a tight crystalline lattice and yet some claims are written in such a way that one skilled in the art would lead to a confusion. Therefore, the reference is still relevant and applicable to the rejection of the claimed invention.

Seven, regarding the ten and eleven arguments, the Examiner has noted applicants' arguments. However, the Wu Gousheng reference does teach that the use of benzene and n-propanol, which are similar to the functionality of the claimed solvents. Furthermore, concerning the particle size, the limitation of a process with respect to ranges of pH, time and particle size does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Particle size is well understood by those of

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ordinary skill in the art to be a result-effective variable , especially when attempting to control selectivity of the intended process.

#### Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Victor Oh whose telephone number is (703) 305-0809. The examiner can normally be reached on 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on (703) 308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

*Victor Oh*  
9/20/03

*Alan L. Rotman*  
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